

## RESEARCH ARTICLE

# Correlation between auditory-vestibular functions and estrogen levels in postmenopausal patients with Meniere's disease

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**Background:** To investigate auditory and vestibular functions, estrogen levels, and its clinical correlation in postmenopausal females with Meniere's disease (MD).

**Methods:** We retrospectively analyzed the serum estradiol (E2) levels and the auditory and vestibular functions measured by auditory brainstem response (ABR) to high click rate, pure-tone audiometry (PTA), and caloric test on postmenopausal women who suffered from MD or not at the Specialist Clinic of Vertigo, Shandong Provincial Hospital, during September 2010 to October 2014.

**Results:** A total of 76 postmenopausal patients with MD and 50 healthy postmenopausal controls were included. The patients with MD had lower estrogen levels ( $22.50 \pm 16.66$  pg/mL vs  $30.69 \pm 18.59$  pg/mL,  $P = 0.011$ ), longer I-V interpeak latency of ABR (left  $0.22 \pm 0.16$  mseconds vs  $0.18 \pm 0.10$  mseconds,  $P = 0.118$ ; right  $0.24 \pm 0.13$  mseconds vs  $0.17 \pm 0.09$  mseconds,  $P = 0.001$ ), and higher unilateral weakness (UW) value ( $P < 0.001$ ) in comparison with the controls. The mean pure-tone thresholds of at the speech frequency (500 Hz, 1 kHz, 2 kHz, and 3 kHz) were significantly elevated in patients with MD than those in the controls (left  $P < 0.001$ , right  $P < 0.01$ ). The estradiol level of patients with MD was correlated with ABR latency (left  $r = -0.229$ ,  $P < 0.05$ ; right  $r = -0.220$ ,  $P < 0.05$ ) and UW value ( $r = -0.328$ ,  $P < 0.05$ ), but not with mean pure-tone threshold.

**Conclusions:** Estrogen levels correlated with auditory and vestibular function in postmenopausal patients with MD. Low estrogen may be involved in the microcirculatory disturbance of the inner ear, affecting the occurrence and development of MD.

**KEYWORDS**

auditory hearing function, estradiol/blood, Meniere's disease, postmenopausal, vestibular function

## 1 | INTRODUCTION

Meniere's disease (MD) is one of the most frequent inner ear diseases characterized by episodes of recurrent vertigo with fluctuating sensorineural hearing loss, pulsatile tinnitus, and aural fullness.<sup>1</sup> It is reported the prevalence of MD in females was higher than that of males.<sup>2</sup> Moreover, MD occurs at any age, but it is more likely to develop in the middle-aged adults (age of

40-60 years).<sup>3</sup> The underlying causes of MD are complex and multifactorial, including sensory, visual, vestibular, neurologic, and age-related changes.<sup>4-6</sup> Also, Hallpike et al<sup>7</sup> found that histopathology of MD was basically changed with hydrolabyrinth (also called endolymphatic hydrops). Corticosteroid, the major medication for sudden hearing loss, Meniere's disease, autoimmune hearing loss, and other auditory system diseases, has been studied for more than 60 years. To date, corticosteroid plays a

significant role in treating sudden hearing loss and other hearing impairment disorders. Despite the research of the mechanism and effectiveness of corticosteroid on inner ears has been carried out for years, the systematic cognition is still lacked in clinical treatment. Moreover, the peak of MD is at 40~60 years old, which is the menopausal period of women. Estrogen, 17 $\beta$ -estradiol (E2), is well known as a reproductive steroid hormone, may facilitate the loss of intravascular fluid into the extravascular space, producing edema, given its neuroactive properties.<sup>8,9</sup> For postmenopausal females, the estrogen levels are sharply reduced because of a permanent loss in ovarian follicles.<sup>10</sup> The role of hormonal factors in causing MD has been controversial, and the contribution of estrogen to MD in females throughout the aging process remains to be elucidated.<sup>11-14</sup> Moreover, the pathogenetic mechanism of MD is not clear. Therefore, our current study aims to investigate the relationship between estrogen levels and the auditory-vestibular functions in postmenopausal females with MD.

## 2 | PATIENTS AND METHODS

### 2.1 | Ethics statement

The use of human clinical materials in this study was approved by the Ethical Committee of the Shandong Provincial Hospital. All patients or their caregivers have provided written informed consent.

### 2.2 | Patients

Postmenopausal patients with MD with single lateral ear who attended the Specialist Clinic of Vertigo at Shandong Provincial Hospital during the period of September 2010 to October 2014 were collected retrospectively. The diagnosis of MD was according to the criteria settled by the American Academy of Otolaryngology-Head and Neck Surgery.<sup>4</sup> Exclusion criteria were (a) a history of hypertension, diabetes mellitus, myocardial infarction, acute cerebrovascular diseases, or liver-kidney diseases; and (b) receiving hormonal therapy within 3 months of the study entry. The patients' serum estradiol (E2) levels and the auditory and vestibular functions were retrospectively retrieved from case records. Fifty age-matched postmenopausal healthy subjects who had no history of MD, no hearing loss, or abnormal caloric test were recruited as healthy controls.

#### 2.2.1 | Estrogen measurement

Overnight fasting venous blood samples were obtained between 8:00 and 9:00 a.m. after the subjects had rested for 20-30 minutes. The blood samples were placed in tubes without anticoagulant and then centrifuged at 100.71g for 15 minutes to separate serum from blood. A USA Beckman Coulter ACCESS Automated Chemiluminescent Immunoassay System was used to measure the serum E2 level.

#### 2.2.2 | ABR protocol

All subjects were tested with a USA IHS intelligent EP tester for high stimulus rate auditory brainstem response (ABR). All of the ABR mentioned in the study belongs to high stimulation rate. High stimulus rate ABR test was recorded using the Intelligent Hearing Systems (IHS) Smart EP system. Electrodes were placed on the vertex (Cz; positive electrode), on both mastoids (Ai and Ac; negative electrodes), and on the forehead (ground). The responses were filtered with a bandpass of 100-2500 Hz. The analysis time was 15 mseconds. The stimuli consisted of 100-mseconds alternating clicks presented monaurally at rates of 11.1/s and 51.1/s. 90 dB nHL intensity levels were used, summing to 2000. Each ear was tested separately. All the responses were replicated. The difference of I-V interval between low stimulation rates (11.1/s) and high stimulation rates (51.1/s) was analyzed. The difference over 0.28 mseconds is considered to be abnormal.

#### 2.2.3 | Caloric reflex test

Caloric test was performed with a French Synapsys Ulmer VNG electronystagmography system with a temperature switch irrigation technique for 24°C and 49°C. Subjects were laying face upwards with the head raised by 30°, keeping the horizontal semicircular canal in a vertical position. Each ear was examined four times using cold and hot air (40 seconds each time). An infrared electronystagmography system was used to record and analyze nystagmus. Temperature test results were calculated using the maximum slow-phase angular velocity, and when unilateral weakness (UW) was more than 20%, caloric response was considered as abnormal. The bithermal caloric test was performed according to Fitzgerald and Hallpike. Each ear was irrigated alternatively with a constant flow of air at 24°C and 49°C for 60 seconds. The response was recorded over 3 minutes, and a 7-minutes interval between each stimulus was respected to avoid cumulative effects. A video-based system was used (Ulmer VNG, v. 1.4; Synapsys, Marseille, France) to acquire and analyze the eye response. The irrigations were delivered randomly in terms of both temperature and side, and no fixation was allowed while recording. The maximum slow-phase velocity (SPV) of nystagmus after each irrigation was calculated, and unilateral weakness (UW) was determined according to Jongkee's formula. In our laboratory, the value of UW <25% was considered to be normal.

#### 2.2.4 | Hearing (Pure-tone average)

Hearing status was obtained with air conduction pure-tone audiometry using postmenopause. The thresholds at frequencies 500 Hz, 1 kHz, 2 kHz, and 3 kHz were carried out in a sound-attenuated testing room. Higher values indicate poorer hearing.

**TABLE 1** Comparison of serum estradiol levels between the MD group and the control group

Parameters	MD (n = 76)	Control (n = 50)	P-value*
Age (y)	51.6 ± 7.0	52.0 ± 7.6	0.762
Estradiol (pg/mL), median (25%-75%)	19.9 (8.1-33.9)	49.8 (15.7-104.7)	<0.001

MD, Meniere's disease.

When the data did not present a normal distribution, the *t* test was replaced by Mann-Whitney rank sum test to compare two groups.

\*Denotes statistical significance ( $P < 0.05$ ), unpaired *t* test.

### 2.3 | Statistical analysis

Data analyses were analyzed with SPSS 19.0 statistical software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD) and compared with unpaired *t* test. Categorical variables were expressed as frequencies and percentages and analyzed with chi-square test where appropriate. Correlation analysis was conducted by Pearson's test. Two-tailed *P* value <0.05 was considered as the statistically significant.

## 3 | RESULTS

A total of 76 postmenopausal patients with MD (average age 51.6 ± 7.0 years) and 50 postmenopausal healthy subjects (average age 52.0 ± 7.6 years) were included in the study. There was no significant difference in average age between patients with MD and normal subjects. The age of menopause in 76 patients was ranged from 42 to 54 years old with a mean age of 48 years. The time since MD was diagnosed was from September 2010 to October 2014. Five patients were diagnosed with bilateral MD and 71 with unilateral MD. All patients were in the anti-active phase of MD when they were tested. Because it was difficult for them in the active phase of MD, they could not bear it. At the same time, the patient has spontaneous nystagmus, which may affect the results of bilateral thermal tests.

Patients with MD presented lower estradiol (E2) levels than the controls (22.50 ± 16.66 pg/mL and 30.69 ± 18.59 pg/mL, respectively,  $P = 0.011$ ; Tables 1 and 3).

Of all the subjects, 53 of 76 patients with MD (69.7%) had abnormal latency of interpeak interval I-V of the ABR test, presenting longer latency of interpeak interval I-V than the controls (left: 0.22 ± 0.16, right: 0.24 ± 0.13 mseconds). Caloric test showed that 51 patients with MD (67.1%) were considered to have vestibular

dysfunction. The average value of unilateral weakness for 76 patients with MD was increased (30.13%±23.46%). Pure-tone audiometry demonstrated that 25 patients with MD (46.05%) were diagnosed with hearing loss. The mean pure-tone audiometric thresholds were 30.84 ± 19.17 dB for the left ear and 34.57 ± 22.87 dB for the right-sided ear in the patients with MD.

Pearson's test showed that the estradiol levels of the patients with MD correlated with I-V interpeak latency of ABR (left  $r = -0.229$ ,  $P = 0.031$ ; right  $r = -0.220$ ,  $P = 0.025$ ) and UW in bithermal caloric test ( $r = -0.328$ ,  $P = 0.027$ ), but not correlated with the mean pure-tone thresholds (left  $r = -0.203$  and right  $r = -0.175$ ;  $P = 0.329$  and 0.417, respectively; Tables 2 and 3).

## 4 | DISCUSSION

Previous studies have reported that decline in estrogen is partly associated with the onset of postmenopausal symptoms and diseases.<sup>15-19</sup> In this study, we studied the correlation between estrogen level and auditory and vestibular function in postmenopausal patients with MD. Results found that the level of estradiol in postmenopausal patients with MD was significantly lower than that in control group. The interval time of ABR I-V wave with high stimulation rate was significantly longer than that of the control group, and the left and right ears were <0.05 with significant difference. Moreover, estradiol level was negatively correlated with high stimulation rate of ABR, which is in line with clinical observations that estrogen is associated with hearing and vestibular systems in postmenopausal women.<sup>20,21</sup> Lower estrogen levels could significantly increase the risk of hearing or longer ABR latencies. It was also reported that postmenopausal women who were administered estrogen therapy have better hearing than those who were not, suggesting that estrogen therapy may slow down hearing loss.<sup>17</sup> Moreover, our preliminary clinical observation suggested

**TABLE 2** Correlations between estradiol level and hearing-vestibular function for the MD group

Pearson's correlation estradiol level	I-V interpeak latency			Pure-tone average	
	Left	Right	UW	Left	Right
<i>r</i>	-0.229	-0.220	-0.328	-0.203	-0.175
<i>P</i> -value*	<0.05	<0.05	<0.05	0.329	0.417

MD, Meniere's disease; UW, unilateral weakness.

\*Denotes statistical significance ( $P < 0.05$ ).

**TABLE 3** Comparison of serum estradiol level between the MD and control groups

Group	NC	E2 (pg/mL)	ABR to high click rate evoked potential (ms)		PTA (dB)		UW (%)
			Left	Right	Left	Right	
Treated group	76	22.50 ± 16.66	0.22 ± 0.16	0.24 ± 0.13	30.84 ± 19.17	34.57 ± 22.87	30.13% ± 23.46%
Control group	50	30.69 ± 18.59	0.18 ± 0.10	0.17 ± 0.09	19.40 ± 4.00	21.35 ± 5.38	15.59% ± 9.58%

NC, number of cases.

that postmenopausal females with MD appeared to have significantly lower estradiol levels and poorer auditory and vestibular functions.

Epidemiological studies have revealed that estrogen regulates vascular endothelial tone, cerebral blood flow, neurotransmitter system, as well as neuroactive metabolites.<sup>18,22-24</sup> Estrogen also has a sodium-water retention function to maintain the ionic and liquid balance of the endolymphatic lymph nodes.<sup>25</sup> Besides that, estrogen could enhance GABA inhibition through GABA<sub>A</sub> synaptic receptors, receptors in brainstem vestibular nucleus, regulating the eyeball movement, vestibular ocular reflex, and vestibular spinal reflex.<sup>26</sup> It was also reported that the risks of postural instability and falling could be reduced by hormone replacement therapy in postmenopausal women.<sup>27</sup> In the present study, most of the postmenopausal females with MD had abnormal auditory brainstem response (69.74%) and unilateral vestibular hypofunction (67.1%). Furthermore, estrogen levels of the postmenopausal females with MD were associated with elevated I-V interpeak latency (worse) and greater unilateral weakness (worse) than the controls. However, we reckoned that such correlation is rather weak (left  $r = -0.229$ , right  $r = -0.220$ ;  $-0.328$ , respectively) although the results were statistically significant. And there was no relationship between estrogen levels and higher pure-tone thresholds in ears. Such results, however, may be associated with our limited number of cases, lack of large sample studies, or the effects of estrogen on the hearing system of animals or humans, which need to be further explored.

The physiological functions of estrogen are mediated through estrogen receptors, the ER $\alpha$  and ER $\beta$ .<sup>9,19</sup> Both of these receptors are found in the inner ear, with ER $\alpha$ -specific localization in the spiral ganglion type I cells and ER $\beta$  in the stria vascularis involved in the ion and fluid balance of the endolymph and cochlear and vestibular sensory transduction.<sup>8,9</sup> Furthermore, expressions of estrogen receptors in the inner ear seem to be modulated by circulating levels of estrogen.<sup>28</sup> Previous animal studies reported that ER $\beta$  knockout mice had severe progressive hearing loss and the female midshipman fish had ER $\alpha$  expression in the inner ear, the auditory mechanism of which could be changed by the estrogen level.<sup>29,30</sup> These contradict a recent study that reported no significant difference in the allelic frequency of ER $\alpha$  polymorphisms between patients with MD and controls (no MD and SSNHLX).<sup>13</sup> Also in this study, the polymorphisms of ER $\alpha$  entailed no significant risk of MD. The underlying reasons for such discrepancies and estrogen effect in Meniere's disease remain to be elucidated.

In conclusion, postmenopausal females with MD presented lower estrogen levels, increased pure-tone thresholds, elevated I-V interpeak latency, and higher incidence of unilateral caloric weakness. Changes of estrogen levels might have contributed to the deterioration symptoms of Meniere's disease (low-frequency hearing loss, episodic symptoms of vertigo, aural fullness, and tinnitus) in postmenopausal females to a certain extent. Future studies would be worthwhile to define the efficacies of proper hormone replacement therapy on postmenopausal patients with MD.

## 5 | BULLET POINT SUMMARY

1. Postmenopausal females with Meniere's disease (MD) presented lower estrogen levels, increased pure-tone thresholds, elevated I-V interpeak latency, and higher incidence of unilateral caloric weakness.
2. Changes of estrogen levels might have contributed to the deterioration symptoms of MD (low-frequency hearing loss, episodic symptoms of vertigo, aural fullness, and tinnitus) in postmenopausal females to a certain extent.
3. Estrogen levels correlated with auditory and vestibular function in postmenopausal patients with MD.
4. Low estrogen may be involved in the microcirculatory disturbance of the inner ear, affecting the occurrence and development of MD.

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